Antimalarial Drugs for the Prevention of Chronic Kidney Disease in Patients with Rheumatoid Arthritis

The Importance of Controlling Chronic Inflammation?

Jennifer C. Rodrigues and Joanne M. Bargman

Clin J Am Soc Nephrol 13: 679–680, 2018. doi: https://doi.org/10.2215/CJN.03300318

Department of Medicine, University of Toronto, Toronto, Ontario, Canada; and Division of Nephrology, University Health Network, Toronto, Ontario, Canada

Correspondence:
Dr. Joanne M. Bargman, Division of Nephrology, University Health Network, 200 Elizabeth Street, Room 8N 840, Toronto, ON, Canada M5G 2C4. Email: Joanne.Bargman@uhn.ca

The pathogenesis of rheumatoid arthritis is a complex interplay between genetic predisposition and immunologic dysregulation. Altered immune response to cigarette smoke and gut microbiota have been implicated in the pathogenesis of the disease. Synovial tissue is an active immunologic site, with multidirectional interactions among fibroblasts, T cells, B cells, and dendritic cells. Dendritic cells produce cytokines that induce the differentiation of inflammatory Th1 and Th17 T cells. Fibroblasts function as antigen-presenting cells and induce the expression of inflammatory cytokines by T cells. B cells produce autoantibodies against a variety of antigens (cyclic-citrillunated proteins, rheumatoid factor), which trigger cytokine expression and participate in bone homeostasis (reviewed in ref. 1).

Rheumatoid arthritis and its treatment have been recognized to be associated with kidney dysfunction. A kidney biopsy series showed that patients with ≥1 g/d of proteinuria had membranous nephropathy or amyloidosis, whereas in those with creatinine ≥1.5 mg/dl, amyloidosis was the most common finding (2). An analysis of United States Renal Data System (USRDS) data, however, showed that the most frequent causes of ESKD in patients with rheumatoid arthritis are still diabetes (33.5%) and hypertension (30.6%), with amyloidosis (0.5%), vasculitis (7.4%), and analgesic nephropathy (0.5%) being relatively uncommon (3). Whether this reflects the inherent limitations of USRDS data compared with kidney biopsy (4) or that associated comorbidities in patients with rheumatoid arthritis are more likely to lead to ESKD is unclear.

Treatment of rheumatoid arthritis consists of anti-inflammatory medications (nonsteroidal anti-inflammatory drugs [NSAIDs] and glucocorticoids [GCs]) in addition to both nonbiologic (hydroxychloroquine, leflunomide, methotrexate, and 5-aminosalicylic acid) and biologic (TNF-α, non–TNF-α inhibitors, and Janus kinase inhibitors) disease-modifying antirheumatic drugs (5). NSAIDs have been associated with higher risk of AKI, acute interstitial nephritis, membranous nephropathy, and chronic kidney dysfunction (reviewed in ref. 6). Penicillamine and gold, older medications used to treat rheumatoid arthritis, have been reported to be a cause of membranous nephropathy (reviewed in ref. 7). NSAIDs, gold, and penicillamine have also been associated with secondary minimal change disease (reviewed in ref. 8); 5-aminosalicylic acid has been linked with acute interstitial nephritis, minimal change disease, and long-term effects on kidney function with some degree of reversibility (reviewed in ref. 9).

Biologic therapies include the TNF-α inhibitors etanercept, infliximab, adalimumab, golimumab, and certolizumab (with varying chemical formulations and affinity for TNF-α, non–TNF-α biologics, such as abatacept [T cell costimulatory molecule inhibitor], rituximab, and tofacitinib [an oral Janus kinase inhibitor]) (5). Kidney side effects, including membranous nephropathy, IgA nephropathy, and lupus nephritis, have all been associated with the TNF-α inhibitors (reviewed in ref. 10). A large cohort study of 4617 patients suggested that patients with rheumatoid arthritis and an eGFR>60 ml/min per 1.73 m^2 had a lower incidence of CKD when treated with biologic agents (hazard ratio, 0.71; 95% confidence interval, 0.53 to 0.94) (11), which may be related to improvement of the chronic inflammatory state.

Antimalarials, including hydroxychloroquine, exert their effects on the immune system through selective suppression of autoantigen presentation on macrophages, inhibition of toll-like receptor signaling, and cytokine expression (reviewed in ref. 12). In patients with rheumatoid arthritis, antimalarials have recently been shown to have cardioprotective effects; a large systematic review and meta-analysis of 35,213 patients in both randomized, controlled trials and cohort studies showed improvement in lipid profiles in users compared with nonusers in addition to a lower incidence of diabetes and cardiovascular disease (13).

In this issue of the *Clinical Journal of the American Society of Nephrology*, the authors (14) report on an observational cohort of 2619 patients with rheumatoid arthritis and no history of CKD, in whom 1212 were receiving hydroxychloroquine. Using International Classification of Diseases (ICD-9) codes, they found that, in those receiving hydroxychloroquine, the incidence of CKD was lower (10.3 versus 13.8 per 1000 person-years; $P=0.03$) in addition to a lower cumulative risk of CKD. Using a Cox proportional hazards model adjusted for demographics, clinic visits, comorbidities, and medications and reporting a subhazard ratio adjusting for the higher mortality of patients with rheumatoid arthritis and CKD,

the lower incidence of CKD persisted in the patients receiving hydroxychloroquine (adjusted hazard ratio, 0.64; 95% confidence interval, 0.45 to 0.90; $P=0.01$). The authors explored their conclusions using propensity matching as well as sensitivity analyses with various definitions of treatment with hydroxychloroquine, diagnosis of rheumatoid arthritis, and inclusion of patients with concomitant SLE and psoriasis and without informative censoring in those who discontinued hydroxychloroquine. There was both a time-dependent effect and a dose-dependent effect of hydroxychloroquine on incident CKD. In their multivariable model, the authors (14) adjusted for the baseline differences in those receiving hydroxychloroquine (increased clinic visits, GC use, and exposure to TNF-α inhibitors).

Within the limitations of an observational cohort, it is interesting to speculate as to whether the associated better adherence to therapy and higher GC use may play a role in hindering the development of incident CKD in this patient population. There is an interesting parallel to a study of carotid intimal-medial thickness in patients with lupus, where the use of hydroxychloroquine and higher (not lower) mean daily GC dose were associated with improved vascular geometry by univariate analysis (15). It is possible that dampening of the chronic inflammatory state mitigates accrual of progressive vascular damage and subsequent kidney impairment.

Although the mechanism underlying the kidney protection associated with antimalarial therapy in people with rheumatoid arthritis is only speculative, it may be mediated through improved microvascular function, including that of the kidneys, as a result of dampening of the chronic inflammatory state. This study highlights the importance of these agents in the rheumatic diseases and underscores the importance of controlling chronic inflammation (14).

Disclosures

J.C.R. is funded by a Vasculitis Clinical Research Consortium - Vasculitis Foundation Clinical Research Fellowship.

References

1. Angelotti F, Parma A, Cafaro G, Capecchi R, Alunno A, Puxeddu I: One year in review 2017: Pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol* 35: 368–378, 2017
2. Makino H, Yoshinaga Y, Yamasaki Y, Morita Y, Hashimoto H, Yamamura M: Renal involvement in rheumatoid arthritis: Analysis of renal biopsy specimens from 100 patients. *Mod Rheumatol* 12: 148–154, 2002
3. Paudyal S, Yang FM, Rice C, Chen CC, Skelton M, Bethel M, Brown S, Nahman NS Jr., Carbone L: End-stage renal disease in patients with rheumatoid arthritis. *Semin Arthritis Rheum* 46: 418–422, 2017
4. Layton JB, Hogan SL, Jennette CE, Kenderes B, Krisher J, Jennette JC, McClellan WM: Discrepancy between Medical Evidence Form 2728 and renal biopsy for glomerular diseases. *Clin J Am Soc Nephrol* 5: 2046–2052, 2010
5. Singh JA, Saag KG, Bridges SL Jr., Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T: 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 68: 1–26, 2016
6. Hörl WH: Nonsteroidal anti-inflammatory drugs and the kidney. *Pharmaceuticals (Basel)* 3: 2291–2321, 2010
7. Jefferson JA, Couser WG: Therapy of membranous nephropathy associated with malignancy and secondary causes. *Semin Nephrol* 23: 400–405, 2003
8. Glassock RJ: Secondary minimal change disease. *Nephrol Dial Transplant* 18[Suppl 6]: vi52–vi58, 2003
9. Gisbert JP, González-Lama Y, Maté J: 5-Aminosalicylates and renal function in inflammatory bowel disease: A systematic review. *Inflamm Bowel Dis* 13: 629–638, 2007
10. Oikonomou KA, Kapsoritakis AN, Stefanidis I, Potamianos SP: Drug-induced nephrotoxicity in inflammatory bowel disease. *Nephron Clin Pract* 119: c89–c94, 2011
11. Sumida K, Molnar MZ, Potukuchi PK, Hassan F, Thomas F, Yamagata K, Kalantar-Zadeh K, Kovesdy CP: Treatment of rheumatoid arthritis with biologic agents lowers the risk of incident chronic kidney disease [published online ahead of print February 3, 2018]. *Kidney Int* doi:10.1016/j.kint.2017.11.025
12. Lee SJ, Silverman E, Bargman JM: The role of antimalarial agents in the treatment of SLE and lupus nephritis. *Nat Rev Nephrol* 7: 718–729, 2011
13. Rempenault C, Combe B, Barnetche T, Gaujoux-Viala C, Lukas C, Morel J, Hua C: Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Ann Rheum Dis* 77: 98–103, 2018
14. Wu C-L, Chang C-C, Kor C-T, Yang T-H, Chiu P-F, Tarng D-C, Hsu C-C: Hydroxychloroquine Use and Risk of CKD in Patients with Rheumatoid Arthritis. *Clin J Am Soc Nephrol* 13: 702–709, 2018
15. Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, Crow MK, Schwartz JE, Paget SA, Devereux RB, Salmon JE: Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 349: 2399–2406, 2003

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Hydroxychloroquine Use and Risk of CKD in Patients with Rheumatoid Arthritis," on pages 702–709.